Atty Dkt no: 213/102-US4

SPECIFIC MODULATION OF TH1/TH2 CYTOKINE EXPRESSION BY RIBAVIRIN IN ACTIVATED T-LYMPHOCYTES

This application is a continuation-in-part of co-pending, allowed US Ser. No. 09/156,646, filed September 18, 1998, which is a continuation in part of US 09/097450, filed June 15, 1998, issued on May 16, 2000 as 6,063,772, which is a continuation of US Ser. No. 08/590449 filed Jan 23, 1996, issued on June 16, 1998 as US 5,767,097.

FIELD OF THE INVENTION

The field of the invention is immunology.

BACKGROUND OF THE INVENTION

From seminal work by Mossman and Coffman (Mossmann TR, Coffmann RL: Th1 and Th2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989, 7: 145-173), growth factors known as cytokines produced by T helper or $CD4^+$ T cells in both human and murine systems were classified into two subsets, Th1 and Th2. These were characterized by their functions in regulating various types of immune responses. Cytokines produced by Th1 cells [interleukin (IL)-2, interferon-alpha (IFNγ), tumor necrosis factor-alpha (TNFα), IL-12] stimulated strong cellular immunity whereas Th2 cytokines [IL-4, IL-5, IL-6, IL-10, IL-13] were important for eliciting humoral (antibody) responses *in vivo*. Recently cytokines produced by non-$CD4^+$ T cells have been shown to be important in *in vivo* responses. In particular, the cytotoxic or $CD8^+$ T cells can also be subdivided into two subgroups, Tc1 and Tc2, which correspond to the same subsets in T helper cells (Carter LL, Dutton RW: Type 1 and Type 2: a functional dichotomy for all T cell subsets. *Curr Opin Immunol* 1996, 8: 336-342). This has led to the current nomenclature being generalized from Th1/Th2 to Type 1/Type 2 to reflect more closely the response generated by particular cytokines, rather than the cell types that produces them.

At the time the original application was filed for the recently issued patent (Specific modulation of Th1/Th2 cytokine expression by ribavirin in activated T cells - R. Tam, #5,767,097), the nomenclature of Type 1 and Type 2 had not been universally adopted. We thus used the Th1/Th2 nomenclature prevalent at the time of the original filing to include both $CD4^+$

and $CD8^+$ T cells, as shown in the 'Background' section of that application (column 1, line 14). In this application we employ the terms, Type 1 and Type 2, instead of the previously used terms, Th1/Th2.

Strongly polarized Type 1 and Type 2 responses not only play different roles in protection, they can promote different immunopathological reactions. Type 1-type responses are involved organ specific autoimmunity such as experimental autoimmune uveoretinitis (Dubey et al, 1991, *Eur Cytokine Network* **2** : 147-152), experimental autoimmune encephalitis (EAE) (Beraud et al, 1991, *Cell Immunol* **133** : 379-389) and insulin dependent diabetes mellitus (Hahn et al,1987, *Eur J Immunol* **18** : 2037-2042), in contact dermatitis (Kapsenberg et al, *Immunol Today* **12** : 392-395), and in some chronic inflammatory disorders. In contrast Type 2-type responses are responsible for triggering allergic atopic disorders (against common environmental allergens) such as allergic asthma (Walker et al, 1992, *Am Rev Resp Dis* **148** : 109-115) and atopic dermatitis (van der Heijden et al, 1991, *J Invest Derm* **97** : 389-394), are thought to exacerbate infection with tissue-dwelling protozoa such as helminths (Finkelman et al, 1991, *Immunoparasitol Today* **12** : A62-66) and Leishmania major (Caceres-Dittmar et al, 1993, *Clin Exp Immunol* **91**: 500-505), are preferentially induced in certain primary immunodeficiencies such as hyper-IgE syndrome (Del Prete et al, 1989, *J Clin Invest* **84**: 1830-1835) and Omenn's syndrome (Schandene et al, 1993, *Eur J Immunol* **23**: 56-60), and are associated with reduced ability to suppress HIV replication (Barker et al, 1995, *Proc Soc Nat Acad Sci USA* **92**: 11135-11139).

Thus, it is clear that modulation of the lymphokine profiles of the aforementioned disease states would be of therapeutic benefit. Promoting a Type 1 response would most likely lead to the reversal of a Type 2 phenotype and vice versa. Monoclonal antibodies (mAb) to lymphokines, lymphokines themselves and other agents such as thiol antioxidants (Jeannin et al, 1995, *J Exp Med* **182**: 1785 - 1792) have been shown to reverse the pathogenesis of certain diseases by inhibiting the disease-promoting cytokine pattern, either Type 1 or Type 2. For example, intracellular protozoan infections are limited by IFNγ but exacerbated by IL-4, while nematode infections are controlled by IL-4 and exacerbated by IFNα (Heinzel et al, 1989, *J Exp Med* **162**: